

# Synthesis of Small Molecule c-Met Tyrosine Kinase Inhibitor Precursors for Development of Potential PET Imaging Agents

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## Background

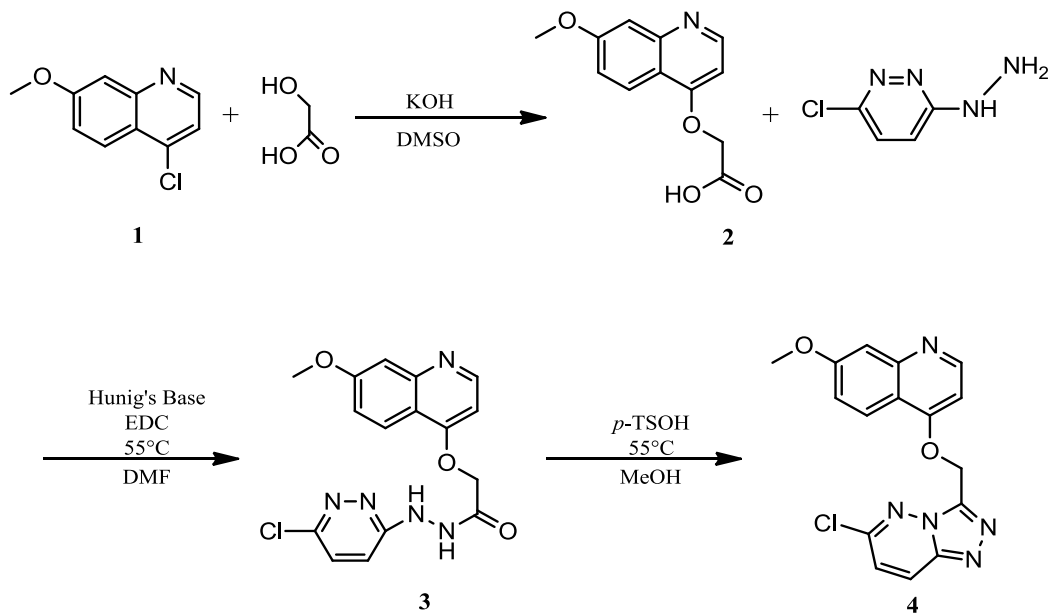
The c-Met tyrosine kinase receptor is located in cell membranes and is a natural receptor for hepatocyte growth factor (HGF).<sup>1,2</sup> C-Met in healthy cells is involved with development in embryos and liver regeneration/wound healing in adults. Deregulation and subsequent overexpression of c-Met has been associated with increased cell proliferation, angiogenesis and metastasis in a variety of cancers. Amplification of c-Met has also been shown to occur as a resistance mechanism in some lung cancer patients that were initially responsive to gefitinib. Inhibition of c-Met returned gefitinib efficacy.<sup>3</sup> A selective c-Met targeting PET imaging agent could be very useful for cancer diagnosis, deciding on a course of therapy with a c-Met inhibitor and/or for monitoring patient response to therapy. In an effort to develop new PET imaging agents able to detect the c-Met receptor a series of compounds has been prepared based on a reported class of highly selective c-Met tyrosine kinase inhibitors derived from a shared triazolopyridazine/quinoline scaffold.<sup>1,2</sup> Compounds prepared include three precursor molecules, which can be radiolabeled with <sup>18</sup>F-fluoride, two final products containing the stable <sup>19</sup>F isotope and one literature standard with known biological activity.<sup>1,2</sup>

## Chemistry

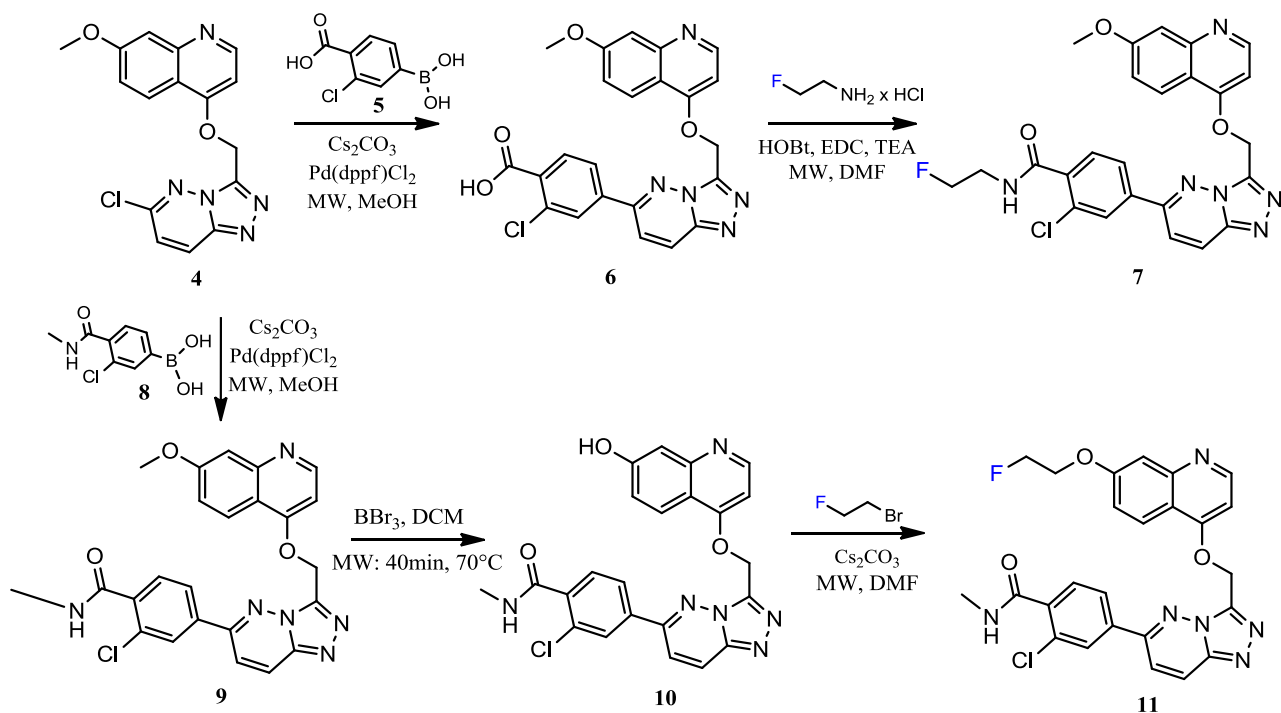
The common intermediate **4** was prepared by literature method starting from 4-chloro-7-methoxyquinoline (Scheme 1). The 4-chloroquinoline derivative **1** was treated with glycolic acid in the presence of potassium hydroxide to yield 2-((7-methoxyquinolin-4-yl)oxy)acetic acid (**2**). The carboxylic derivative **2** was then coupled to 1-(6-chloropyridazin-3-yl)hydrazine giving *N*-(6-chloropyridazin-3-yl)-2-((7-methoxyquinolin-4-yl)oxy)acetohydrazide (**3**). Formation of

the cyclic triazolopyridazine intermediate **4** was accomplished by an acid catalyzed ring closure. The chloro-triazolopyridazine **4** was used in palladium catalyzed coupling reactions to synthesize the array of requested compounds as illustrated in Scheme 2.

**Scheme 1.** Synthesis of common intermediate **4**.

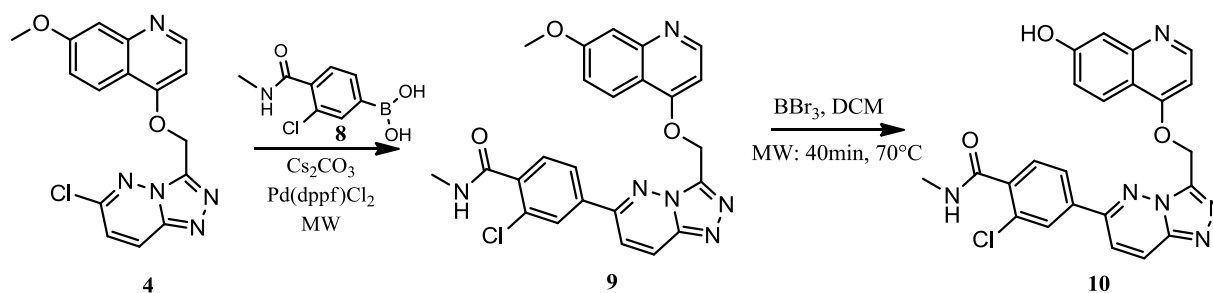


**Scheme 2.** Syntheses of cold standards (**7**, **9** and **11**) and precursors for radiolabeling (**6** and **10**)

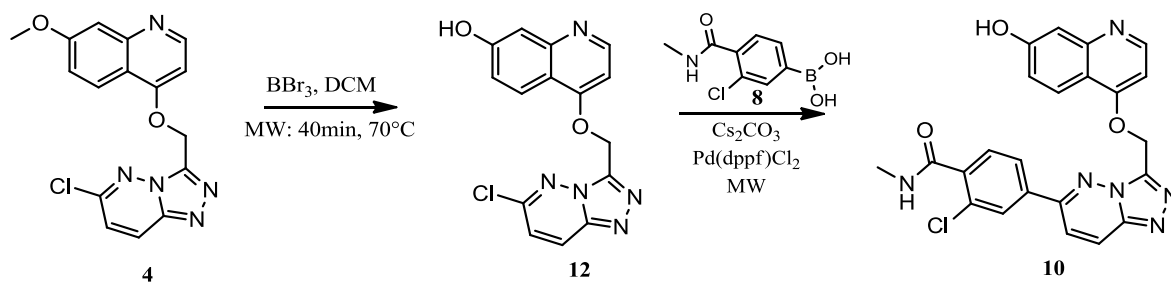


The literature method applied Suzuki coupling reaction of **4** and both 4-carboxy-3-chlorophenylboronic acid (**5**) and 3-chloro-4-(*N*-methylcarbamoyl)phenylboronic acid (**8**) in the presence of tri-*t*-butylphosphonium tetrafluoroborate, cesium carbonate ( $\text{Cs}_2\text{CO}_3$ ), and tris(dibenzylideneacetone)dipalladium(0) ( $\text{Pd}_2(\text{dba})_3$ ) catalyst.<sup>1</sup> Attempts to synthesize compounds **6** and **9** following the literature method failed in our hands. The electron-rich nature of the triazolopyridazine ring and the electron-poor nature of both boronic acids make these compounds unfavorable for Suzuki coupling.<sup>4</sup> Several palladium catalysts were tested for effectiveness under an array of different conditions including palladium(II) acetate ( $\text{Pd}(\text{OAc})_2$ ),  $\text{Pd}_2(\text{dba})_3$ , tetrakis(triphenylphosphine)palladium(0) ( $\text{Pd}(\text{PPh}_3)_4$ ) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride complex with dichloromethane ( $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$ ). Various solvents including 1,4-dioxane, dimethylformamide (DMF), ethanol, methanol, acetonitrile and dimethoxyethane were tested along with cesium carbonate, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, dipotassium phosphate, triethylamine, and potassium *tert*-butoxide as potential bases.  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$  gave by far the best results for both boronic acids.  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$  was an effective catalyst with alcohols as solvents. Several byproducts were consistently generated including substitution of chlorine with a proton and substitution of chlorine with an ether bond corresponding with the alcohol solvent (methoxy group for methanol and ethoxy group for ethanol). These byproducts could not be entirely avoided, but their formation was effected by concentration of reagents, base selection, reaction time and reaction temperature. The optimal conditions for the preparation of both derivatives **6** and **9** were found to be  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$  as a catalyst with  $\text{Cs}_2\text{CO}_3$  in methanol heated to 100°C for 30 minutes under microwave irradiation. From precursor **6** an amide bond was formed with 2-fluoroethylamine hydrochloride yielding cold standard **7**.

**Scheme 3.** Suzuki coupling followed by methoxy group deprotection strategy



**Scheme 4:** Methoxy group deprotection followed by Suzuki coupling strategy



Two approaches were investigated to obtain compound **10** from the common intermediate **4**. In the first approach the Suzuki coupling of **4** and **8** was carried out first, followed by methyl ether **9** deprotection (Scheme 3). The second approach is shown in Scheme 4 and involves deprotection of the methyl ether **4** followed by Suzuki coupling of the resulting 4-((6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methoxy)quinolin-7-ol (**12**) to boronic acid **8**. The intermediate **12** was especially difficult to perform Suzuki coupling on due to low solubility in most suitable solvents, including methanol. Both approaches were successful leading to formation of **10** in moderate to low yields. However, the synthetic Scheme 3 was found to give a significantly higher yield than synthetic Scheme 4 and thus was followed to prepare **10** on the desired scale.

Compound **9** was successfully prepared following the synthetic scheme 2 by Suzuki coupling under the universal conditions established.

To deprotect the methoxy group of **9** in order to obtain compound **10**, several methods and reaction schemes were tried. The main concern when attempting to deprotect the methoxy group was the sensitive ether linkage between the quinoline and triazolopyridazine groups. First deprotection using 1-dodecanethiol was tried, but it deprotected the ether linkage much more easily than the methoxy group. Next deprotection in concentrated hydrobromic acid was

attempted. Selective deprotection was achieved, but with significant decomposition and substitution of the chlorine with bromine. Finally, 1M boron tribromide in anhydrous dichloromethane ( $\text{BBr}_3 \cdot \text{DCM}$ ) was tried. Under temperatures ranging from  $-78^\circ\text{C}$  to room temperature, no reaction was observed. However, the selective deprotection of the methyl ether was achieved using unreported conditions of 1M boron tribromide in dichloromethane at elevated temperature applying microwave irradiation.

Compound **11** was obtained by the coupling of compound **10** to 1-fluoro-2-bromoethane as shown in Scheme 2.

Amphoteric compounds encountered during the synthesis such as **10** and particularly **6** presented solubility and purification challenges. Compound **6** exhibited poor or no solubility in most common solvents, which made purification of the complex reaction mixture especially difficult. Purification by solvent extraction led to formation of emulsions of the product and undesired byproducts between layers. The emulsion could not be avoided by switching the organic solvent to dichloromethane, ethyl acetate or chloroform. Attempts at flash purification also failed to isolate compound **5** in a desirable purity. Waters Sep-Pak<sup>®</sup> Vac C18 20cc (5g) cartridges proved to be effective at isolating the product from both the non-polar byproducts and catalyst residues. All compounds were of at least 95% purity.

## Experimental

**General:** All organic precursors and solvents were obtained from commercial sources and used as received unless otherwise noted. Thin-Layer Chromatography (TLC) analyses were performed with Analtech (Newark, DE) silica gel GHLF 0.25mm plates using UV and iodine detection. Flash chromatography was performed on a Teledyne Isco CombiFlash Companion instrument with UV detection at 254nm. Analytical HPLC analysis were performed on an Agilent 1200 Series instruments equipped with multi wavelength detectors using an Agilent Eclipse Plus C18 column (4.6x50mm, 3.5 $\mu\text{m}$ ) with a flow rate of 1 mL/min. Solvent A was 0.05%TFA in water, Solvent B was 0.05%TFA in ACN, and a linear gradient of 5 %B to 95 %B over 10 min was used. APCI mass spectrometry was performed on 6130 Quadrupole LC/MS Agilent Technologies instrument equipped with diode array detector.  $^1\text{H}$ -NMR spectra were recorded with a Varian spectrometer operating at 400MHz. Chemical shifts are reported in parts per

million ( $\delta$ ) and are referenced to tetramethylsilane (TMS). Microwave reactions were performed in a CEM Discover<sup>®</sup> microwave oven.

**2-((7-Methoxyquinolin-4-yl)oxy)acetate (2).**<sup>1</sup> To a solution of glycolic acid (150 g, 1.97 mol) in DMSO (150 mL) in a 3L-4-neck flask potassium hydroxide (KOH) pellets (172 g, 3.07 mol) were added in few portions with mechanical stirring. Initially, 60 g of the KOH was added and the reaction slowly warmed to 50 °C followed by additional 15 g portions of KOH added every few minutes. At 50 °C a potassium salt of glycolic acid precipitated. As more KOH was added and the temperature reached 75°C, the salt was solubilized. After KOH addition was completed, water (7.5 mL) was added to compensate for steam loss. In a separate round bottom flask, a solution of 4-chloro-7-methoxyquinoline (75 g, 389 mmol) in anhydrous DMSO (220 mL) was stirred at 60 °C and then added to the potassium glycolate in one portion. The reaction mixture was heated to 150 °C with a heating mantle for 2 hours at which time all starting material had been consumed, which was verified by HPLC analysis. The reaction mixture was cooled in an ice bath leading to the formation of a brown suspension. Water (1.5 L) was added to the crude reaction mixture, followed by 6 M hydrochloric acid bringing the pH to 4 at which point a tan precipitate formed. The solid was then filtered off under vacuum. The resulting tan solid was slurried with a mixture of water and acetonitrile (7:3) (100 mL), filtered and washed with water (3 x 75 mL) and acetonitrile (2 x 50 mL). The resulting powder was dried under high-vacuum overnight yielding **2** (47 g, 52% yield). <sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  8.63 (d, 1H,  $J$  = 5.2 Hz), 8.08 (d, 1H,  $J$  = 9.2 Hz), 7.33 (d, 1H,  $J$  = 2.4 Hz), 7.21 (dd, 1H,  $J$  = 2.6 and 9 Hz), 6.80 (d, 1H,  $J$  = 5.2 Hz), 4.96 (s, 2H, CH<sub>2</sub>), 3.91 (s, 3H, OCH<sub>3</sub>). MS ( $m/z$ ): 234.1 (M+H)<sup>+</sup>.

**N'-(6-Chloropyridazin-3-yl)-2-((7-methoxyquinolin-4-yl)oxy)acetohydrazide (3).**<sup>1</sup> To a 500 mL round bottom flask containing **2**-((7-methoxyquinolin-4-yl)oxy)acetate (22 g, 94 mmol, 1 eq), anhydrous DMF (190 mL) was added under argon via cannula. Hunig's base (50 mL, 287 mmol, 3 eq) was then added via cannula under argon followed by the addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC-HCl) (23.5 g, 122 mmol, 1.3 eq) and hydroxybenzotriazole (HOBt) hydrate (14.5 g, 94 mmol, 1 eq). The mixture was stirred for 15 minutes to allow activation of the carboxylic acid. 1-(6-chloropyridazin-3-yl)hydrazine (13.7 g, 94 mmol, 1 eq) was added and the mixture was then heated to 55°C for 2.5 hours under constant stirring. The reaction contents were then poured onto ice water (400 mL) and allowed to stir for

30 minutes. The resulting orange suspension was filtered off and washed with water leading to the formation of a water-impermeable cake, preventing further filtering. The cake was then scraped out and suspended in water (400 mL) by stirring overnight. The foamy suspension was then easily filtered off followed by washing with diethyl ether (300 mL). The resulting tan solid was dried under high-vacuum overnight yielding **3** (19 g, 56% yield). <sup>1</sup>H NMR (400 MHz, DMSO): δ 10.46 (s, 1H), 9.72 (s, 1H), 8.74 (d, 1H, *J* = 5.2 Hz), 8.34 (d, 1H, *J* = 9.2 Hz), 7.58 (d, 1H, *J* = 9.6 Hz), 7.36 (d, 1H, *J* = 2.8 Hz), 7.27 (dd, 1H, *J* = 2.4 and 9.2 Hz), 7.11 (s, 1H), 7.00 (s, 1H), 5.04 (s, 2H, CH<sub>2</sub>), 3.93 (s, 3H, OCH<sub>3</sub>). MS (*m/z*): 360.0 (M+H)<sup>+</sup>.

**4-((6-Chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methoxy)-7-methoxyquinoline (4).** <sup>1</sup>N'-(6-chloropyridazin-3-yl)-2-((7-methoxyquinolin-4-yl)oxy)acetohydrazide (**3**) (18.4 g, 51 mmol, 1 eq) was slurried with methanol (700 mL) and mechanically stirred. The reaction mixture was heated to 55 °C and *p*-toluenesulfonic acid (9.72 g, 51 mmol, 1 eq) was added by funnel in one portion. Immediately after the addition of *p*-toluenesulfonic acid, the reaction mixture turned from a tan slurry to a burnt-orange solution. The temperature was maintained at 55 °C for 15 hours at which point 90% of the starting material had cyclized and the mixture was allowed to cool to room temperature. The solvent was removed by rotary evaporation yielding a dark brown oil. Acetonitrile (200 mL) was added and the resulting suspension was filtered through a funnel with a cotton ball. The remaining solid was taken up in methanol and once again removed by rotary evaporation to yield a tan solid. Acetonitrile (200 mL) was added and filtered through a funnel with a cotton ball. The two acetonitrile solutions were combined and the pH was brought to 10 by dropwise addition of 1 M NaOH at which point a white solid precipitated. The resulting solid was filtered off and washed with water (200 mL) and acetonitrile (100 mL) to yield an off-white solid, **4** (10.47 g, 60% yield). <sup>1</sup>H NMR (400 MHz, DMSO): δ 8.72 (d, 1H, *J* = 5.2 Hz), 8.56 (d, 1H, *J* = 9.6 Hz), 7.96 (d, 1H, *J* = 9.2 Hz), 7.61 (d, 1H, *J* = 9.6 Hz), 7.34 (d, 1H, *J* = 2.4 Hz), 7.26 (d, 1H, *J* = 5.2 Hz), 7.12 (dd, 1H, *J* = 2.8 and 9.2 Hz), 5.90 (s, 2H, CH<sub>2</sub>), 3.90 (s, 3H, OCH<sub>3</sub>). MS (*m/z*): 342.1 (M+H)<sup>+</sup>.

**2-Chloro-4-(3-(((7-methoxyquinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)benzoic acid (6).** 4-((6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methoxy)-7-methoxyquinoline (**4**) (700 mg, 2.05 mmol, 1 eq), 4-carboxy-3-chlorophenylboronic acid (**5**) (532 mg, 2.65 mmol, 1.3 eq), Cs<sub>2</sub>CO<sub>3</sub> (1.34 g, 4.1 mmol, 2 eq) and Pd(dppf)Cl<sub>2</sub>•DCM (252 mg, 309 μmol, 0.15 eq) were dissolved in anhydrous methanol (27 mL) in a 35 mL microwave vial.

The contents were briefly stirred on a stir plate to ensure there were no chunks of palladium on the walls of the vial. The reaction mixture was heated at 100 °C for 30 minutes at 150 W in a microwave oven. The solvent was evaporated and the resulting residue was resuspended in chloroform (75 mL) and then water (50 mL) was added. Upon shaking, 3 layers formed with water on top, chloroform on the bottom and a thick suspension in the middle. The bottom chloroform layer and the middle suspension were collected and solvent was removed by rotary evaporation. Further purification was accomplished using 5g (20cc) Waters Sep-Pak<sup>®</sup> cartridges. Cartridges were conditioned with acetonitrile (60 mL) followed by water (80 mL). Impure product (300 mg) was dissolved in DMSO (400 µL), diluted with water (1.1 mL) and then sonicated and vortexed. The resulting suspension was then loaded to the Sep-Pak<sup>®</sup> cartridge with extra water. The Sep-Pak<sup>®</sup> cartridge was washed with water until the eluting drops lacked color. Acetonitrile was then used until the eluent had no color and then finally the Sep-Pak<sup>®</sup> was washed with methanol. The methanol fractions contained the product accompanied with an unidentified aliphatic impurity. The aliphatic impurity was removed by treating the product with dichloromethane overnight followed by filtration and drying under vacuum yielding compound **6** (660 mg, 70% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.68 (d, 1H, *J* = 4 Hz), 8.35 (d, 1H, *J* = 9.6 Hz), 7.93-8.11 (m, 4H), 7.55 (d, 1H, *J* = 7.2 Hz), 7.30 (s, 1H, CH), 7.14 (d, 1H, *J* = 8 Hz), 6.06 (s, 2H, CH<sub>2</sub>), 3.93 (s, 1H, OCH<sub>3</sub>). MS (*m/z*): 462.0 (M+H)<sup>+</sup>.

**2-Chloro-*N*-(2-fluoroethyl)-4-(3-(((7-methoxyquinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)benzamide (7).** To a flame dried round bottom flask 2-chloro-4-(3-(((7-methoxyquinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)benzoic acid (**6**) (200 mg, 433 µmol, 1 eq), HOBT hydrate (100 mg, 655 µmol, 1.5 eq), EDC•HCl (125 mg, 655 µmol, 1.5 eq) and triethylamine (240 µL, 1.73 mmol, 4 eq) were added and dissolved in DMF (2 mL). The mixture was stirred for 30 minutes and 2-fluoroethylamine-HCl (52 mg, 522 µmol, 1.2 eq) was added. The reaction mixture was stirred under positive pressure of argon for 24 hours. The crude reaction mixture was poured onto ice water (14 mL) and stirred for 30 minutes. The product was extracted into CHCl<sub>3</sub> (15 mL). The organic layer was washed with water (2 x 15 mL) followed by brine (1 x 15 mL), dried over magnesium sulfate (MgSO<sub>4</sub>) and the solvent was evaporated. The crude product was further purified by flash chromatography using chloroform and 5% ammonium in methanol, yielding **7** (175 mg, 80% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.71 (d, 1H, *J* = 5.6 Hz), 8.26 (d, 1H, *J* = 10), 8.05 (d, 1H, *J* = 9.2 Hz), 7.97 (s, 1H), 7.80 (m,



2H), 7.59-7.61 (m, 1H), 7.34 (d, 1H,  $J = 2.4$  Hz), 7.11 (d, 1H,  $J = 5.6$  Hz), 7.03 (dd, 1H,  $J = 2.4$  and 9.2 Hz), 6.70 (br s, 1H, NH), 5.95 (s, 2H,  $CH_2$ ), 4.63 (dt, 2H,  $J = 4.7$  and 47.6 Hz), 3.90 (s, 3H,  $OCH_3$ ), 3.82 (dq, 2H,  $J = 4.8$  and 28 Hz). MS ( $m/z$ ): 507.1 ( $M+H$ )<sup>+</sup>.

**2-Chloro-4-(3-(((7-hydroxyquinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-*N*-methylbenzamide (9).** To a solution of 4-((6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methoxy)-7-methoxyquinoline (**4**) (500 mg, 1.46 mmol, 1 eq), 3-chloro-4-(*N*-methylcarbamoyl)phenylboronic acid (**8**) (400 mg, 1.87 mmol, 1.3 eq),  $CS_2CO_3$  (950 mg, 2.91 mmol, 2 eq) and  $Pd(dppf)Cl_2 \cdot DCM$  (200 mg, 245  $\mu$ mol, 0.17 eq) were dissolved in methanol (27 mL) in a 35 mL microwave flask. The contents were briefly stirred to ensure there were no chunks of palladium on the walls of the flask. The reaction mixture was heated in a microwave oven at 100°C for 30 minutes at 150W. The solvent was then evaporated and the crude product was resuspended in chloroform (50 mL). The solution was washed with water (3 x 40 mL) followed by brine, dried over  $MgSO_4$  and the solvent was evaporated. The resulting solid was purified by flash chromatography using chloroform and 5% ammonia in methanol, yielding **9** (305 mg, 55% yield). <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.72 (d, 1H,  $J = 5.2$  Hz), 8.27 (d, 1H,  $J = 10$  Hz), 8.06 (d, 1H,  $J = 9.2$  Hz), 7.97 (s, 1H), 7.83 (d, 2H,  $J = 2.8$  Hz), 7.61 (d, 1H,  $J = 9.6$  Hz), 7.35 (d, 1H,  $J = 2.4$  Hz), 7.10 (m, 2H), 5.95 (s, 2H,  $CH_2$ ), 3.91 (s, 1H,  $OCH_3$ ), 3.06 (s, 1H,  $NCH_3$ ) MS ( $m/z$ ): 475.1 ( $M+H$ )<sup>+</sup>.

**2-Chloro-4-(3-(((7-hydroxyquinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-*N*-methylbenzamid (10).** 2-chloro-4-(3-(((7-methoxyquinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-*N*-methylbenzamide (**9**) (600 mg, 1.26  $\mu$ mol, 1 eq) was dissolved in 1M boron tribromide in anhydrous dichloromethane ( $BBr_3 \cdot DCM$ ) (15 mL) in a 30 mL microwave vial and heated for 40 minutes in a microwave oven at 70 °C and 150 W. After completion, water (25 mL) was added to decompose any remaining  $BBr_3$ . The reaction mixture was brought to pH 8 via the addition of saturated aq.  $Na_2CO_3$ . An extraction was carried out with chloroform yielding an emulsion between a lower chloroform layer and a clear water layer on top. The chloroform layer and the emulsion were co-evaporated and purified by flash chromatography with chloroform and methanol, yielding **10** (524 mg, 90% yield). <sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  10.07 (s, 1H) 8.61 (m, 1H), 8.53 (m, 1H) 8.42 (s, 1H) 8.16 (s, 1H), 8.10 (m, 2H) 7.88 (m, 1H) 7.56 (m, 1H), 7.15 (m, 2H), 7.01 (m, 1H), (5.99 (s, 2H,  $CH_2$ ), 2.73 (s, 3H,  $CH_3$ ) MS ( $m/z$ ): 461.1 ( $M+H$ )<sup>+</sup>.

**2-chloro-4-(3-(((7-(2-fluoroethoxy)quinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-*N*-methylbenzamide (11).** A 10 mL microwave vial was charged with 2-chloro-4-(3-(((7-hydroxyquinolin-4-yl)oxy)methyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-*N*-methylbenzamide (**10**) (200 mg, 434  $\mu$ mol, 1 eq), Cs<sub>2</sub>CO<sub>3</sub> (212 mg, 650  $\mu$ mol, 1.5 eq) followed by addition of anhydrous DMF (5 mL). 1-bromo-2-fluoroethane (63  $\mu$ L, 2 eq) was then added and the reaction mixture was heated in a microwave oven at 100 °C and 150 W for 10 minutes. The reaction mixture was poured onto ice water (50 mL), stirred for 30 minutes and extracted with chloroform. The chloroform layer was washed with water (3 x 30 mL) and brine (1 x 30 mL), dried over MgSO<sub>4</sub>, and solvent was evaporated. The resulting solid was purified by flash chromatography using chloroform and 5% ammonium in methanol, yielding **11** (182 mg, 83% yield). <sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  8.71 (d, 1H, *J* = 5.2 Hz), 8.56 (d, 1H, *J* = 10 Hz), 8.42 (d, 1H, *J* = 4.4 Hz), 8.153 (s, 1H, NH), 8.10 (d, 1H, *J* = 9.6 Hz), 8.06 (dd, 1H, *J* = 1.4 and 8.2 Hz), 7.98 (d, 1H, *J* = 8.8 Hz), 7.56 (d, 1H, *J* = 8 Hz), 7.35 (d, 1H, *J* = 2.4 Hz), 7.31 (d, 1H, *J* = 5.2 Hz), 7.15 (dd, 1H, *J* = 2.4 and 9.2 Hz), 6.03 (s, 2H, CH<sub>2</sub>), 4.77 (dt, 2H, *J* = 3.7 and 47.6 Hz), 4.36 (dt, 2H, CH<sub>2</sub>, *J* = 3.6 and 30 Hz), 2.741 (s, 3H, NCH<sub>3</sub>). MS (*m/z*): 507.1 (M+H)<sup>+</sup>.

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